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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/051,986	01/15/2002	Jennifer L. Hillman	PF-0168-3 DIV	3139

22428 7590 10/21/2004

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EXAMINER	
MITRA, RITA	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 10/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/051,986	HILLMAN ET AL.	
	Examiner	Art Unit	
	Rita Mitra	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-9,11,12,14,16,17,20,23,26,28,29,31 and 48* is/are pending in the application.

4a) Of the above claim(s) *4-9,11,12,14,16,20,23,26,28,29,31,48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/15/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Applicant's response to office action dated June 30, 2004 and election of Group I, claims 1 and 17 with traverse in the reply filed on July 29, 2004 is acknowledged. The grounds on which the traversal is made that the examination and search of SEQ ID NO: 1 and SEQ ID NO: 4 within group I is not unduly burdensome. Arguments are found persuasive, therefore SEQ ID NO: 1 and SEQ ID NO: 4 would be examined under current prosecution. Claims 4-9, 11, 12, 14, 16, 20, 23, 26, 28, 29, 31 and 48 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Therefore, claims 1 and 17 are currently pending and are under examination.

Claim Rejections - 35 USC § 112, First Paragraph, Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polypeptide comprising an amino acid sequence as set forth in SEQ ID NO: 1 or in SEQ ID NO: 4, does not reasonably provide enablement for the amino acid sequence comprising an amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO: 1 or SEQ ID NO: 4, or for any fragments thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as

routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The inventions are drawn to encompass Ras proteins, referred to collectively as "RASP" and individually as RASP-1 (polypeptide comprising of sequence of SEQ ID NO: 1) or (RASP-4 (polypeptide comprising of sequence of SEQ ID NO: 4); polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to SEQ ID NO: 1 and SEQ ID NO: 4; biologically active fragments and immunogenic fragments thereof. Despite knowledge in the art for the isolation of polypeptides , the specification fails to provide guidance regarding how to isolate the fragments and variants of SEQ ID NO: 1 or 4. It is *a priori* unknown and unpredictable as to which of the enormous number of organisms which exist possess polypeptide having the sequence of SEQ ID NO: 1 or 4 or fragments and variants thereof.

In the instant case, the amount of experimentation is enormous since the number of changes from the specific sequence are large, one of skill in the art would have to make and test each one to determine if it had the Ras protein activity of the parent protein. The amount of guidance presented is limited to the exact sequence. No discussion is present as to where the changes might be made to SEQ ID No: 1, much less any sequence that encodes SEQ ID No: 1. An example of desirable guidance for a DNA encoding a protein would be disclosure of the sequence of exons and introns, regulatory sequences, binding sites for transcription factors, active sites in the coding sequence. These are not present. The nature of the invention is a new polypeptide sequence corresponding to a Ras family protein. The art is unpredictable. The effect of one or a few conservative substitutions might be somewhat predictable, if the active

areas of the molecule were known, but more changes than that, are less predictable. The number of changes to result in a sequence with 90% identity to the starting sequence would, of course, be 10 changes per hundred nucleotides. The effect on function of this many changes is clearly unpredictable. Finally, these claims are very broad in the sense that many millions of different proteins fall within the scope of the claims.
Based on this analysis, the finding of undue experimentation is mandated.

These claims are also not enabled because there would be no reason to expect a polypeptide that is 90% identical to SEQ ID No: 1 or 4, or any fragment of SEQ ID NO: 1 or 4 would have the specific characteristics of the claimed Ras, thus be indistinguishable from another Ras.

The instant claims (e.g. claims 1, 17) are drawn to, inter alia, biologically active fragments and immunogenic fragments of polypeptide sequences of Ras proteins in SEQ ID NO: 1 and SEQ ID NO: 4. The specification defines "biologically active," as to a protein having structural, regulatory, or biochemical functions of a naturally occurring molecule (page 10, lines 12-13). However, the specification provides inadequate guidance to allow the skilled artisan to determine, without undue experimentation, which of the myriad possible modified sequence of RASP would be likely to retain biological activity. The specification provides no working examples of RASP 'fragments ' to show the effects of modifying peptide sequence of the native protein, nor does the specification provide guidance regarding, for example, sequence of the domain structure of the protein (except RASP-1 has a region which resembles signature sequence of the GTP-binding domain, page 18, lines 14-16) or addition or removal or modification of the domain, the location of the active site (except stated as 'potential' active cites, page 18, lines 22-25). The binding activity of the RASP protein is based solely on the basis of sequence similarities to known GTP binding proteins. However, the claimed protein shares 75% sequence identity with mouse LMW GTP-binding protein Rah (page 18, lines 25-27). Without further evidence clearly demonstrating that the polypeptides or the fragments actually bind guanine nucleotides, their designation as GTP- binding proteins remains to be seen.

In order to predict with reasonable assurance the effect that different modification are likely to have on the protein, and thereby predict which variants will retain biological activity,

the skilled artisan would require data regarding, for example, the molecular basis of the protein's activity, its secondary and tertiary structure and the relative importance of any domains of the protein in maintaining said activity. The instant specification provides insufficient guidance to allow the skilled artisan to predict beforehand the effects of particular modification on RASP. Since inadequate guidance is provided to allow prediction of the effect of a given modification, determination of the full spectrum of RASP variants that would have the activity of the wild-type protein would require that the skilled artisan make and test a large number of the possible variants.

The specification indicates at page 10, lines 13-16 that "immunologically active" referes to the capability of the natural, recombinant, or synthetic RASP, or of any oligopeptide thereof, to induce a specific immune response in appropriate animals or cells and to bind with specific antibodies. Since detailed information regarding the structural, functional and biological activity of the claimed polypeptide fragments are lacking, it is unpredictable as to whether the oligopeptide fragments can be used to induce a specific immune response and to bind with specific antibodies.

Claim 17 is also not enabled because of the limitation 'composition.' The reasoning for this is identical to that for the "fragments" rejection above. It would require undue experimentation to determine which of the many possible fragments of sequence in SEQ ID NO: 1 or SEQ ID NO: 4 might have any function at all. The specification is silent as to how to use any such fragment and thus these claims are not enabled.

Based on this analysis, the finding of undue experimentation is mandated.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Morimoto et al. (Genes & Development, Vol. 5, pp 2386-2391, 1991). The reference teaches a low molecular (LMW) GTP-binding protein that appears to be the first member of a new class of G protein. This G protein was cloned from the HT4 neural cell line and has the closest homology to the rab, sec4 and ypt1 members of the LMW G proteins. The reference also teaches an unique feature that distinguishes this G protein from other LMW G proteins is its carboxy-terminal amino acid sequence –Cys-Cys-Pro (see abstract). This G protein has 94.9% sequence identity to SEQ ID NO: 1, (see alignment result 2, Database: SwissProt_42, Accession NO: Q64008). Morimoto's LMW G protein is considered for the polypeptide sequence comprising amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1 and also having a –Cys-Cys-Pro sequence at its carboxy terminus (claim 1).

This G protein of Morimoto also has 93.8% sequence identity with amino acid sequence set forth in SEQ ID NO: 4, (see alignment result 2, Database: SwissProt_42, Accession NO: Q64008). Morimoto's LMW G protein is considered for the polypeptide sequence comprising amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1 and also having a –Cys-Cys-Pro sequence at its carboxy terminus (claim 1).

Morimoto's protein suspended into water or appropriate buffer while characterizing the protein, is considered for the composition comprising the polypeptide of claim 1 of instant application (claim 17). Therefore, claims 1 and 17 of the instant application are being anticipated by Morimoto et al.

Conclusion

No claims are allowed.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Rita Mitra whose telephone number is (571) 272-0954. The Examiner can normally be reached from 9:30 a.m. to 6:30 p.m. on weekdays. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Jon Weber, can be reached at (571) 272-0925. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette,1096 OG 30 (November 15, 1989). The Fax Center number is (703) 872-9306. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0547.

Rita Mitra, Ph.D.
October 8, 2004

JON WEBER
SUPERVISORY PATENT EXAMINER